

Gonadectomy in Complete Androgen Insensitivity Syndrome: Why and When?

Ulla Döhnert^a Lutz Wunsch^b Olaf Hiort^a

^aDivision of Paediatric Endocrinology and Diabetes, Department of Paediatrics and Adolescent Medicine, and

^bDepartment of Paediatric Surgery, University of Lübeck, Lübeck, Germany

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Abstract

Prophylactic gonadectomy has been recommended in complete androgen insensitivity syndrome (CAIS) because of an increased risk for the development of malignant germ cell tumors in the intra-abdominal gonads. No reliable screening parameters are available to detect early (pre-)malignant changes. Because the tumor risk before puberty is very low, the timing of gonadectomy has been postponed to allow spontaneous puberty and involvement of the patients in important decisions affecting their body and health. Gonadectomy after puberty is still discussed controversially. There are difficulties in determining the absolute malignancy risk for individuals with CAIS, difficulties with hormone therapy, and lack of studies supporting different protocols. In contrast, endogenous hormone profiles show very specific features that influence bone health, psychosocial well-being, and many other aspects which still have to be investigated. For women with CAIS who wish to keep their gonads, we propose a biannual screening program which has to be evaluated in a prospective multi-center trial.

Complete androgen insensitivity syndrome (CAIS) is characterized by a complete external female genital appearance despite a 46,XY karyotype and unrestricted testicular development with functioning Leydig cells [Hughes et al., 2012]. The underlying condition is a peripheral resistance towards all androgenic steroids due to a mutation of the androgen receptor. This leads to a very specific endocrine environment with slightly elevated LH levels and FSH, testosterone, and estradiol values in the male reference range despite pubertal feminization [Doehnert et al., 2015].

The current debate on the prophylactic gonadectomy versus the saving of the testes is inflamed by several points. As reviewed by Cools et al. [this issue], an increased risk for testicular germ cell tumors (GCT) has been demonstrated. However, support groups and patients are fighting for keeping their gonads based on their personal experience of unphysiological hormone replacement after gonadectomy. Furthermore, they condemn the violation of bodily integrity through gonadectomy. Therefore, this debate has to consider the medical arguments and the ethical implications of a life-changing procedure in a patient cohort with a rare medical condition.

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Current Arguments against Gonadectomy

The essential argument for gonadectomy in CAIS is the prevention of malignant degeneration of the intra-abdominal or inguinal gonads. As explained by Cools et al. [this issue], there is an increased incidence of germ cell neoplasia in situ (GCNIS) in the gonads of people with both CAIS and PAIS (partial androgen insensitivity syndrome) compared to the general male population [Manuel et al., 1976; Rutgers and Scully, 1991; Cools et al., 2016]. The exact determination of the incidence of (pre-)malignant gonadal tumors in CAIS has, however, been impeded by early gonadectomy, lack of confirmation of diagnosis by sequencing of the *AR* gene, unknown numbers of undiagnosed healthy women with CAIS, and further study and publication bias [Deans et al., 2012].

Progression of GCNIS to invasive GCT is assumed to be obligatory in the general population. Differences in pathophysiology leading to a potentially lower risk in CAIS have been explained [Kaprova-Pleskacova et al., 2013; Cools et al., 2016]. Supporting this hypothesis, most of the unsuspected lesions found at gonadectomy are histologically classified as GCNIS [Cheikhelard et al., 2008; Nakhil et al., 2013; Cools et al., this issue]. Reported malignant tumors comprise mostly seminomas and few others like malignant Leydig cell tumor and mixed GCT [Sakai et al., 2000; Iwamoto et al., 2005; Shahidi and Robia, 2007; Herman et al., 2010; Tsubamoto et al., 2013]. Stage 1 GCT can be managed by surgical removal and surveillance alone, and prognosis is very good with survival rates close to 100% [Ehrlich et al., 2015].

Current Arguments for Gonadectomy

Gonads can be localized and investigated by modern imaging techniques. In the first line, this is best achieved by ultrasound (US). In CAIS, the testes-like features like size and shape as well as the low echogenicity and vascular structure are often readily detected, whereas müllerian structures are more difficult to identify. As already discussed by Cools et al. [this issue], there are nonspecific markers of malignant changes as microlithiasis in combination with heterogeneous echogenicity which have only been evaluated for gonads without DSD [Elzinga-Tinke et al., 2010]. Further investigation by magnetic resonance imaging (MRI) can reveal localization of intra-abdominal gonads and genital duct anatomy. There have not been any studies comparing US and MRI, and correlations of

early invasive GCT in CAIS are unknown in both techniques [Nakhil et al., 2013]. If a gonad cannot be detected or a gonadal tumor is suspected, laparoscopy is needed for detailed assessment [Wünsch and Buchholz, 2014]. GCNIS or early invasive GCT can only be diagnosed by a gonadal biopsy, which will result in gonadectomy [Wünsch, 2012].

The Dilemma of Gonadectomy

If gonadectomy is considered, an informed consent must be obtained. The surgeons' responsibility is to assess the individual balance of risks and benefits and to explain this to the patient. The lack of evidence and individual patient-related factors such as insight, the general perception of tumor risk, the availability of qualified health care, and the body constitution have to be considered. Thus, decision making about gonadectomy should be considered as a time-consuming process, and the patient should have an active time-intensive role. The postponement of eventual gonadectomy into adult age is a major advance. Not only does it allow spontaneous puberty to occur, more importantly it permits informed and authoritative decision-making by the patient.

The occurrence of an inguinal hernia during childhood should not be taken as an indication for early gonadectomy. The hernia should be repaired and the gonad fixed to the internal inguinal ring or repositioned into the abdomen. The risk of gonadectomy includes the risks of general anesthesia and those of laparoscopy. Both risks are very low, and laparoscopic gonadectomy can be done as an outpatient procedure. Bilateral gonadectomy takes approximately 30–45 min. Laparoscopy also allows biopsies or gonadopexy, and, moreover, gonadectomy leaves almost no visible scar.

If gonadectomy is postponed, many new questions arise. How does endocrine function develop in adulthood, and when does it decline? How many germ cell tumors will occur, and how will they affect the lives of the patients?

After gonadectomy, continuous and long-term hormone therapy is necessary to achieve induction of puberty and maintenance of sexual function, psychosocial well-being, and bone health [Bertelloni et al., 2011]. So far, there have not been any studies reported that examine different hormonal medications, their dosage, and routes of administration necessary to obtain these aims. In addition, compliance with hormone therapy is widely variable, depending on health-related education, medical care, and well-being.

Patients and support groups have explicitly pointed out the aspects of bodily harm exerted by gonadectomy and problems with unphysiological hormone replacement therapy [Cools et al., 2016]. Still the impact of gonadectomy and hormone therapy has only been addressed in few studies on long-term outcome [Wisniewski et al., 2000; Minto et al., 2003]. Most of the studies included none or only few participants with intact gonads so that results could not be compared either. Existing studies show an impairment of sexual function in women with CAIS [Minto et al., 2003; Köhler et al., 2012] and a higher degree of psychosocial distress [D'Alberton et al., 2015], while female identity and behavior and general quality of life do not differ significantly from other women [Wisniewski et al., 2000; Hines et al., 2003; Minto et al., 2003].

Studies of small populations of women with CAIS reveal an elevated risk of developing reduced bone mineral density under hormone replacement, mostly estrogen therapy, compared with endogenous hormone production in intact gonads [Bertelloni et al., 2010; Meriggiola et al., 2015]. Further studies have to examine the clinical relevance of reduced bone mineral density and possibilities of adopting hormone therapy accordingly. Bone health therefore represents an important issue regarding long-term morbidity after gonadectomy. The influence of gonadectomy on other metabolic parameters affecting cardiovascular morbidity might be relevant as well [Dati et al., 2009].

Recently, we have examined the very specific endocrine profiles of women with CAIS [Doehnert et al., 2015]. A conclusion towards “irregular” or “abnormal” cannot be made in this condition as the usual male/female pattern is lacking and therefore a reference population does not exist. Presumably, further steroids and hormones secreted

in the testes contribute to a complex milieu influencing body functions. Among others, testicular INSL3 [Ferlin et al., 2013] has been demonstrated to affect bone mineralization as outlined by Bertelloni et al. [this issue].

Proposal for a Screening

At this time, it is mostly agreed that gonadectomy in CAIS children prior to puberty is not warranted on a prophylactic basis. These children should undergo their usual pubertal development with endogenous hormone synthesis and should be informed about their condition in due course.

With respect to a potentially increased risk of malignancy after puberty, gonadectomy at this stage should still be the first-line recommendation. However, difficulties of determining the malignancy risk as well as problems of hormone therapy after gonadectomy must be discussed with the patients. For women who wish to keep their gonads, we propose a regular (bi-)annual screening program comprising gonadal imaging by US or MRT, depending on the size and localisation of the gonad, determination of tumor markers (alpha-fetoprotein, beta-HCG, LDH, and optionally PLAP in non-smokers), and endocrine evaluation (LH, FSH, testosterone, and inhibin B). Again, it has to be stressed that no specific and sensitive parameters exist for early detection of (pre-)malignant changes in the gonads so that in other high-risk populations (e.g., for ovarian cancer) early gonadectomy is still recommended. Accordingly, laparoscopy with gonadal biopsy and possibly gonadectomy will be necessary in any woman with CAIS and suspicious findings in the screening. Such a study protocol should be investigated in a prospective multi-center trial.

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